Combination of Curcuminoid with Acupressure for Inflammation and Pain in Elderly People with Osteoarthritis Genu: Protocol for a Randomized Controlled Trial

Srinalesti Mahanani, Nyoman Kertia, Ema Madyaningrum

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Srinalesti Mahanani[1, 2] SKep, Ns, MKep; Nyoman Kertia[3, 4] Prof Dr; Ema Madyaningrum[5] PhD

[1]Doctorate Program of Medical and Health Science, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada Yogyakarta ID
[2]Nursing Department, STIKES RS Baptis Kediri Kediri ID
[3]Department of Internal Medicine, Faculty of Medicine Public Health and Nursing Gadjah Mada University Yogyakarta ID
[4]Dr. Sardjito General Hospital Yogyakarta ID
[5]Department of Mental and Community Health Nursing, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada Yogyakarta ID

Corresponding Author:
Nyoman Kertia Prof Dr
Department of Internal Medicine, Faculty of Medicine Public Health and Nursing
Gadjah Mada University
Jl. Kesehatan Sendowo No.1, Sendowo, Sinduadi, Kec. Mlati, Kabupaten Sleman
Yogyakarta
ID

Abstract

Background: Curcuminoids and acupressure have beneficial effects in reducing pain and inflammation in patients with Osteoarthritis. However, only a few clinical trials are investigating biomarkers to prove this objectively

Objective: This study aimed to investigate the efficacy of acupressure and curcuminoids to inflammatory markers and pain in elderly with Osteoarthritis Genu.

Methods: Randomized controlled trial was conducted among elderly with Osteoarthritis. All participants were randomized to divided into the group with 30 mg curcuminoids from turmeric extract capsules and acupressure (group 1) or the group with placebo and sham acupressure (group 2) for 3 weeks.

Results: The study was approved by the research ethics board and Clinical Trials.gov had reviewed this protocol under Registration number: NCT06105840. The extracts were manufactured from May 2023 to June 2023. Participant recruitment was conducted in September-October 2023, a total of 72 participants aged over 60 years had participated of whom 75.0% (n=54) were female. Data was analyzed in April of 2024, and dissemination of results by the end of 2024.

Conclusions: Primary outcomes were assessed at baseline and after intervention and related to inflammatory markers, endorphin hormones, and cycloxygenase-2 hormone in the blood. Additionally, secondary outcomes included pain, ability to activity daily living, and quality of life. The beneficial effects that may be found in this trial can be exceptionally relevant in clinical practice, justifying this scientific question. The benefits of herbs and acupressure can be helpful to additional options in treating inflammation and pain in patients with Osteoarthritis. Clinical Trial: The ethics research committee has approved the study protocol registered with the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) (project number KE-FK-0674-EC-2023). The study was conducted according to Indonesia's 2021 National Health Research and Development Ethical Guidelines and Standards by the Health Research and Development Ethics Committee and the Helsinki Declaration, revised in 2013. Clinical Trials.gov has reviewed this protocol under Registration number: NCT06105840.

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Trial Registration :

ClinicalTrials.gov NCT06105840 (https://classic.clinicaltrials.gov/ct2/show/NCT06105840)

Keywords: Osteoarthritis; Acupressure; Curcuma; Endorphins; Biomarkers;

Introduction

Background

One of the degenerative processes that occurs in elderly involves the musculoskeletal system. These deteriorations include bone loss and decreased joint fluid volume exacerbated by bearing the body's weight, which can cause elderly people to experience pain. [1] The experience of prolonged pain in patients with osteoarthritis is considered unendurable and reflected in the common cliché, ‘reaching the breaking point’, which describes the experience/process of living with unremitting pain, limitations in mobility, leisure, and social activities, and the resulting negative consequences for the patient's physical and psychological well-being. [2]. These patients with osteoarthritis often seek some turning point for positive changes in their quality of life and relief from the incessant pain. The development of complementary nursing knowledge continues to be carried out, including in the Energy and Biofield Therapies and Biologically Based Therapies groups as Complementary Alternative Medicine (CAM). People aged 50 years and older are likely to be using CAM. Common use of CAM as a complement to conventional medicine—and the high use of multiple prescription drugs—further underscores the need for health care providers and clients/patients/families to have an open dialogue to ensure safe and appropriate integrated health care. [3]. One of the common therapies practiced in many Asian communities, especially the Javanese, is acupressure, a traditional development of massage. Historically, massage is an action that people often do independently which can psychologically make patients feel relief and more comfortable, but research needs to be conducted empirically to ensure its effectiveness.

The pain experienced in patients with osteoarthritis affects many areas of their quality of life, including physical function, emotional behavior, and mental health. Osteoarthritis-related pain is a significant factor in poor quality of life. The most common pharmacological treatment to control pain is using non-steroidal anti-inflammatory drugs, but these drugs have a considerable risk of causing side effects. [4]. Limitations associated with pharmacological treatment result in patients choosing commonly available alternative therapies for pain management. Popular alternative therapies include herbal therapy, therapeutic touch, relaxation techniques, music therapy, acupuncture, and acupressure. Unlike the use of drugs, this alternative therapy does not produce dangerous side effects [5].

Research concerning the effectiveness of herbal therapy on patients with inflammatory osteoarthritis was conducted in Indonesia by Kertia on 80 sufferers. [6]. The results showed that administration of turmeric rhizome extract curcuminoids significantly suppressed the activity of synovial fluid monocytes to secrete cyclooxygenase-2 (COX-2) and reactive oxygen intermediate, as well as reduced leukocyte numbers and fluid malondialdehyde levels. Synovia reduces osteoarthritis-related joint pain, with an ability that is not significantly different compared to diclofenac sodium therapy 3x25 mg per day. Recently, Bertorio [7] conducted research on the development of herbal therapy for osteoarthritis and demonstrated that the

combination of ginger, ginger, soybean, and shrimp shell extracts provided significant results in reducing joint pain, stiffness, and physical disability. The findings were evaluated based on The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and did not show a significant difference when compared with meloxicam.

Recently, research was conducted in several countries to evaluate the effectiveness of acupressure therapy for the pain of patients with osteoarthritis. The study by Alinaghizadeh [8] involved 40 patients with osteoarthritis who were divided into two groups (intervention and control). In the intervention group, acupressure therapy was given for five days for 30 minutes each time. The results showed that the average pain score in the intervention group decreased significantly from 5.89 at the beginning to 4.11 at the end of the study, while the pain score did not change substantially in the control group. These findings remained consistent after adjusting for age, weight, and pretreatment covariates. This study supports the evidence that acupressure therapy provides an effective option for short-term knee pain relief in patients with knee osteoarthritis. In line with the results of Alinaghizadeh's research Akbarznezhad conducted research on 51 elderly persons with osteoarthritis. [9]. Participants were divided into three groups (acupressure intervention, placebo, and controls). The findings of this study revealed that those who received acupressure therapy for 3-4 weeks, for 10-15 minutes each time, showed a significant reduction in the total Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, pain, and physical dysfunction.

Osteoarthritis with the joint disfigurement will cause continues pain that impacts on the increase in medicine consumption, so that it needs to consider alternative complementary therapies in reducing pain. [10] Management of osteoarthritis still need improvement. To date, no research has combined standardized curcuminoid turmeric extract therapy with acupressure for inflammation and pain in patients with osteoarthritis. More clinical trials with appropriate methodology are needed to confirm the effectiveness of standardized turmeric extract, curcuminoids, and acupressure in treating physical problems in patients with osteoarthritis.

Purpose

This study aimed to investigate the efficacy of acupressure and standardized curcuminoids from turmeric extract to reduce inflammatory markers and pain, and endorphin hormones in the blood, while increasing quality of life in elderly patients with Osteoarthritis Genu.

Methods

Study Objective

Primary objective

This study aimed to determine the effectiveness of a combination of two regimens (acupressure and

curcuminoid) as measured by changes from baseline (BL) in leukocytes, neutrophil leukocyte ratio, blood sedimentation rate, pain, secretion of COX-2 and endorphin hormones in the blood compared to placebo after three weeks of treatment in elderly patients with osteoarthritis.

Secondary objectives

The secondary outcomes included pain, ability of activity daily living, and quality of life. Pain was assessed with a Visual Analog Scale. The ability of daily living was assessed with Barthel Index and WOMAC index. The quality of life was measured by respondents' satisfaction in daily activities based on indicators on the Knee injury and Osteoarthritis Outcome Score (KOOS) instrument.

Study design

We conducted a 2-arm, double-blind (patient and investigational blinded) Randomized Controlled Trial (RCT) to assess the efficacy, tolerability, and safety combination of acupressure and curcuminoid versus placebo.

Pre-Screening

Patients were pre-screened for specific x-ray and laboratory parameters. Following a screening visit, eligible subjects entered the washout. After the washout period, eligible subjects were randomized and treated for 3 weeks. The total duration of the study lasted 5 weeks.

Study setting and source population

Eligible participants were individuals recruited from communities covered by government-owned primary care hospitals who consulted a rheumatology subspecialist physician with symptoms of pain and discomfort around the knee.

Participants were recruited from August 2023 to October 2023. An informed consent form was provided to participants in their local language to gain credibility. To maintain the secrecy of data gathering, participant codes were provided, restricting access to only the lead researcher. After obtaining agreement from the participants, a thorough screening process was conducted to determine their eligibility.

Population

The study population consists of male and female patients (≥65 years old) with osteoarthritis (osteoarthritis with knee joint pain, knee joint stiffness in the morning less than 30 minutes, crepitus, deformity, joint swelling (right and left asymmetrical), and other signs of inflammation (a feeling of even warmth and reddish color). The objective was to achieve a random allocation of about 70 patients. Given an

anticipated screening failure rate of 25% and a washout failure rate of 20%, a total of about 100 patients were subjected to screening procedures.

Inclusion criteria

In order to be considered for participation in this study, patients must satisfy all of the following requirements :

1. Clinical diagnosis of Osteoarthritis which was confirmed by physical examination and X-rays;
2. Experience pain with a Numeric Rating scale of 1-7;
3. Must be able to swallow capsules; and
4. Must be able to carry out mobility without assistance or with minimal assistance

Exclusion criteria

Patients fulfilling the following criteria were not eligible for inclusion in this study. The investigator may apply no additional exclusions to ensure the study population represents all eligible patients.

1. Parkinson's disease
2. Dementia disease
3. Psychosis disease
4. New bone fractures
5. Joint dislocations
6. Cancer
7. Rheumatic diseases other than Osteoarthritis (rheumatoid arthritis)
8. Undergoing joint replacement therapy
9. Analgesic dependent disease

Eligibility test procedure

Radiographs were used to assess participants for Osteoarthritis using the Kellgren and Lawrence criteria, which divide osteoarthritis from mild to severe. It should be noted that at the beginning of the disease, the radiographic appearance of the joint still looks normal. According to Kellgren and Lawrence, radiologically, osteoarthritis is classified as follows:

1) Grade 0: Normal, no signs of Osteoarthritis;

2) Grade 1: Doubtful, without osteophytes, doubtful joint narrowing;

3) Grade 2: Minimal, few osteophytes on the tibia and patella and the joint surface is asymmetrically narrowed;

4) Grade 3: Moderate, moderate osteophytes are in several places, the joint surface is narrowed, and subchondral sclerosis appears; and

5) Grade 4: Severe presence of large osteophytes, complete narrowing of the joint surface, severe subchondral sclerosis, and joint surface damage.

The Mini Mental State Examination (MMSE) test was used to assess the patient's cognitive abilities, which is essential to ensure that patients can understand the treatment and outcome measurement process instructions.

Randomization, allocation and blinding

Seventy eligible participants were randomized to the group with curcuminoid capsules and Acupressure (C+A; group 1) or the group with placebo and sham acupressure (P+S; group 2) via lottery randomization. Following this, the individuals were assigned randomly to either the C+A or P+S groups. Figure 1 displays the schematic CONSORT (Consolidated Standards of Reporting Trials) [11] flow diagram for the study procedure, as reported in the study.

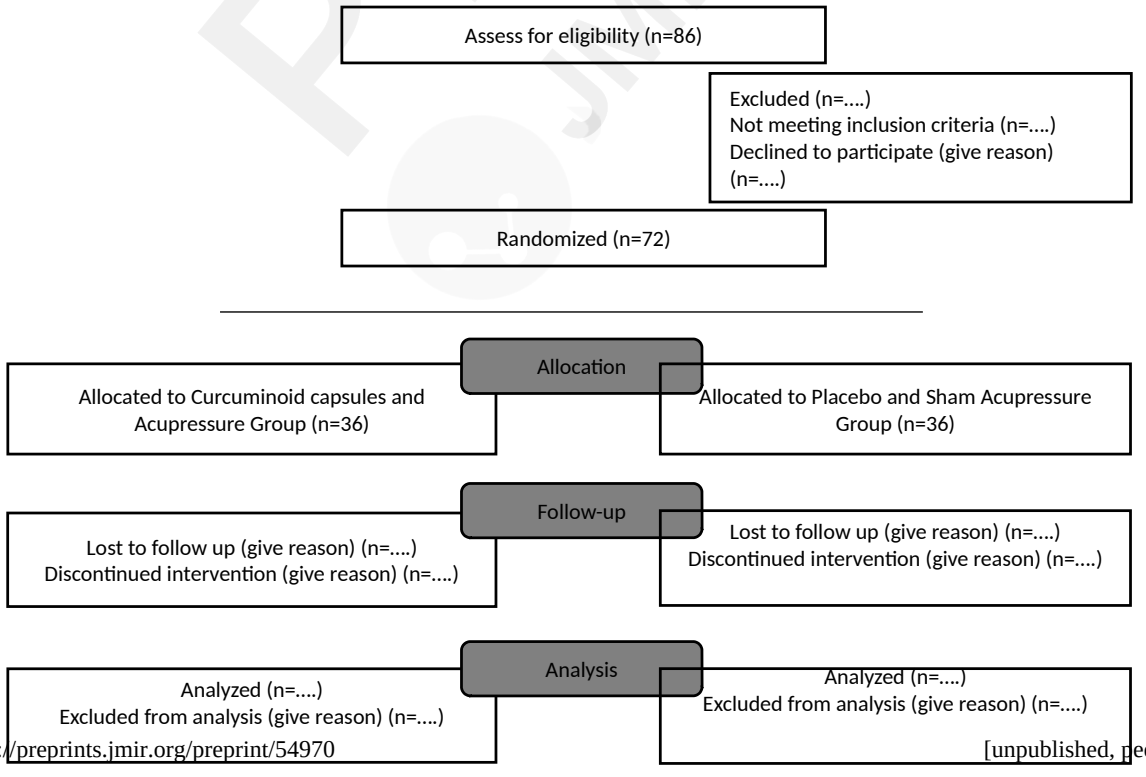

Figure 1. Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

The baseline (BL) characteristics for each participant were determined by the therapist using a standardized assessment form. During the measurement of BL, various data were documented, including sex, age, body mass, pain characteristics, history of sickness, and medication usage. The timetable of participant participation was developed in accordance with Figure 2 of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement. [12]. The primary and secondary outcome indicators were assessed prior to administering the intervention.

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation			Close-out			
TIMEPOINT**		0	*1st week*	*2nd week*	*3rd week*	*1st day*	*1st week*	*2nd week*	*Post 3rd week*
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
[Radiography and MMSE Test]	X								
Allocation		X							
INTERVENTIONS:									
[C+A Therapy]			X	X	X				
[P+S Therapy]			X	X	X				
ASSESSMENTS:									
[Demographic Details]	X								
[Inflammatory Marker]						X			X
[Endorphin]						X			X
[Quality of Life]						X	X	X	X

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommended schedule for participation.

Intervention

Following the administration of standardized evaluations and baseline measurements, the intervention was implemented. The participants were grouped randomly to either the Curcuminoid and Acupressure Therapy (C+A Therapy group) or the Plasebo and Sham Acupressure Therapy (P+S Therapy group) in a random manner. In the study, both the Acupressure Therapy and Sham Acupressure groups underwent a total of two sessions each week, each lasting 20 minutes, for a period of three consecutive weeks. During this period, participants were prohibited from regularly using any medications, with the exception of antihypertensive agents, thyroid meds, and antidiabetic therapies. The participants were provided with electronic message reminders in order

to facilitate their adherence to the intervention. Pre-intervention session reminder texts were dispatched prior to each session. Each participant consumed Curcuminoid capsules and placebo three times daily for a duration of 21 days.

In Acupressure to perform C+A Therapy Group, the patient is put in the supine position with legs straight. The tools and materials were prepared such as a seat (or bed), warm water, olive oil, wet and dry tissue, and towels. The therapist washed their hands, and the participant sat in a comfortable position. The patients were taught breathing relaxation techniques to use during therapy. The patients were allowed to pray according to their respective beliefs. To ensure the participant was relaxed and comfortable, some of the client's clothing or accessories were removed that may hinder the acupressure action being performed, if necessary. Perform a client pain assessment. The parts to be massaged were wiped with warm water treated with a disinfectant solution using a small towel, then dried with a clean towel. Using cream or oil, a warming massage was done with basic massage techniques, according to the client's condition (using rubbing, squeezing, and/or pressing) and stretching the patient's feet. Acupressure massage points are performed at ST34, ST36, Tai Xi Acupoint, GB34, SP 9, SP 8

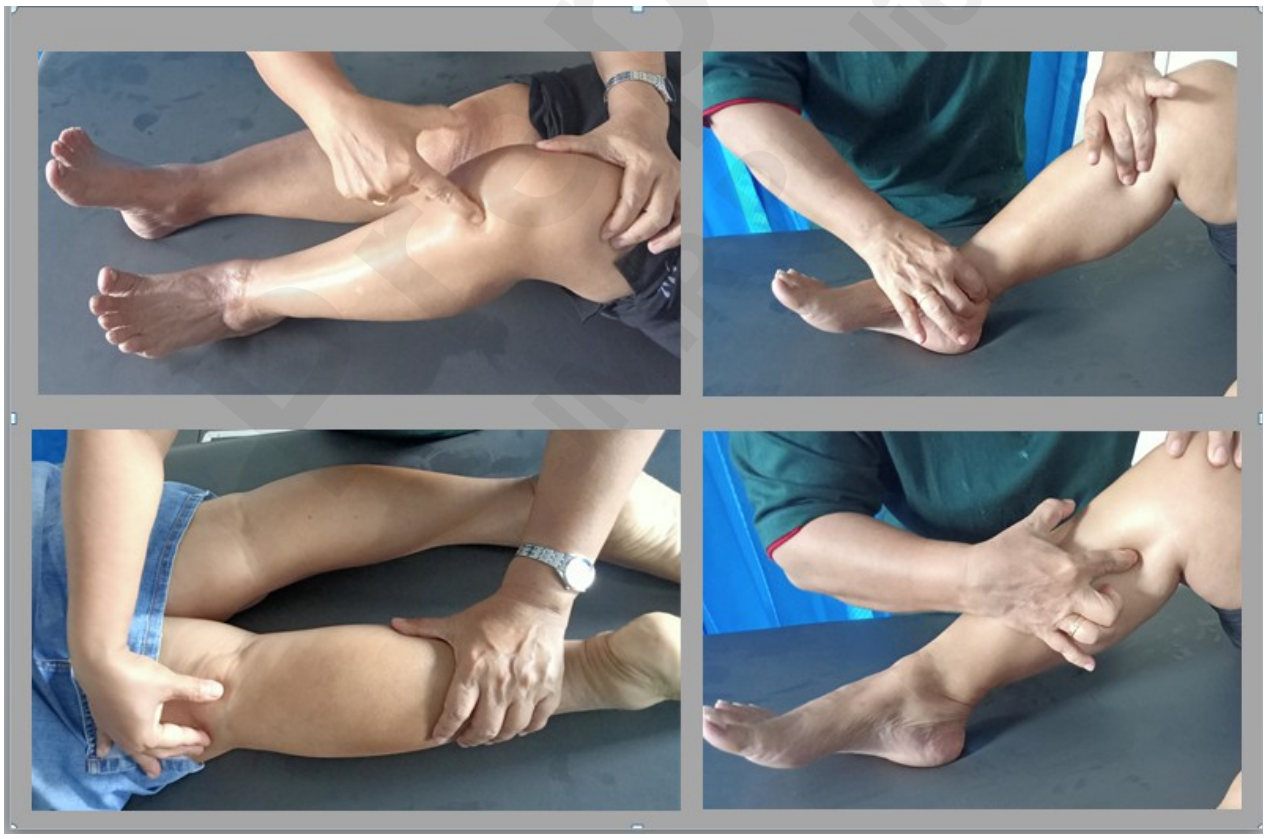

Figure 3. Acupressure massage points

There are 6 points of Sham Acupressure that is given to P+S Therapy group, they are given to the feet area but avoid the therapeutic points used for the C+A Therapy group.

The patient was asked to report any abnormal sensations or discomfort during intervention. The researchers provided the double-blind study medication for the Curcuminoid and Placebo groups. The standardized curcuminoid turmeric extract was prepared. Samples were first made from extracted turmeric and then optimized. The capsule formulation is made from turmeric rhizome extract, which contains 30 mg of curcuminoids per capsule. In the study, standardized curcuminoid turmeric extract was given in capsules 3 times a day for three weeks.

Researcher had confirmed that respondent did not use the other intervention by carrying out routine anamnesis through visiting respondent's house one by one twice in a week which was helped by village health worker (kader) and therapist.

Study Outcomes

All outcome measures were assessed at baseline (BL) and after three weeks of intervention.

Primary Outcomes

1) Inflammatory Markers

Leukocyte numbers,the Neutrophil Lymphocyte Ratio (NLR) and blood sediment rate were measured as inflammation markers. The examination uses a complete blood test using a Hematology Analyzer, a laboratory tool used to measure and count the number of blood cells. The blood samples were mixed using a mixture of reagents to create a hemolyzing process. This process was divided into several purposes in order to measure leukocytes, neutrophils, platelets and erythrocytes.

2) Secretion of the COX-2 enzyme

The COX-2 enzyme is an essential mediator in increasing the inflammatory response. In the blood plasma of patients with osteoarthritis, the COX-2 enzyme can be detected. The COX-2 enzyme examination was conducted using the Enzyme Linked Immunosorbent Assay (ELISA) method on blood plasma

3) Secretion of endorphin hormones

Endorphins, in this case beta endorphin, are hormones released by the pituitary gland in response to stress or pain, which are also secreted in blood plasma. Endorphin hormone levels in the blood were measured before starting therapy and after three weeks of therapy.

Endorphin hormone examination was done using the ELISA method on blood plasma that has been incubated at room temperature for 10-20 minutes, and then the tube was centrifuged for 20 minutes at a speed of 2000-3000 rpm.

Secondary outcomes

The effectiveness of therapy is the ability of the therapy regimen given to suppress several other expected output indicators. Other output indicators were measured before starting therapy and after 3 weeks of therapy

1) Knee pain as measured by the VAS score

2) The WOMAC score assesses joint stiffness and joint functional ability.

WOMAC is a questionnaire developed by Bellamy [13] and continues to be developed to measure the functional abilities of patients with knee osteoarthritis. The WOMAC instrument has been translated into Indonesian. It has been tested for validity by Karsten [14] with Cronbach's alpha coefficient of 0.966 results, indicating relatively high internal consistency. It is highly correlated, meaning that the WOMAC questionnaire in Indonesian is correct. Validated and can be used by the Indonesian people. This questionnaire can evaluate 3 subscales, namely : pain (5 items), stiffness (2 items) and physical function (17 items) by scoring on a 5-point ordinal scale. The details of the scores are pain: score 0 "no pain", score 1 "mild pain", score 2 "moderate pain" score 3 "severe pain" and score 4 "very severe pain"; stiff: score 0 "not stiff", score 1 "mildly stiff", score 2 "medium stiff", score 3 "extremely stiff" and score 4 "stiff to the point of locking"; and physical function: score 0 "not difficult", score 1 "somewhat difficult", score 2 "quite difficult", score 3 "very difficult" and score 4 "very difficult". Range of subscale scores for pain (0-20), stiffness (0-8) and physical function (0-68). The total score is obtained by adding up the scores of the 3 subscales, with a maximum score of 96. A higher WOMAC score indicates pain, stiffness and worse physical function. The total WOMAC score can be categorized into 3 groups, namely low risk (score ≤ 60), moderate risk (score 60-80) and high risk (score ≥ 81).

3) The ability of activity daily living in elderly as assessed by the Barthel Index

The Barthel Index questionnaire was first developed in 1965 by Mahoney. [15] The Maryland State Medical Society holds the inventory of this instrument. Then in 2020, Pongantung [16] translated it into Indonesian and conducted a validity test with the result that inter-rater reliability was satisfactory.

Regarding content validity, the Indonesian version of the Barthel Index is acceptable. The construct validity test revealed two main factors: functional performance and physiological function.

4) Quality of Life assessed with KOOS

KOOS is an instrument to assess patient opinions about the condition of the knee and problems related to the knee. KOOS has been translated into Indonesian and tested for validity by Phatama [17] with Cronbach α results of 0.84 to 0.97 for all subscales, indicating adequate internal consistency. The test-retest reliability demonstrated a high level of accuracy, as indicated by the intraclass correlation coefficients ranging from 0.91 to 0.99 across all subscales. There were no statistically significant variations observed in the replies of the KOOS subscales between the initial administration of the questionnaire and the subsequent administration

within a span of 21 days. The validity and reliability of the Indonesian adaptation of the KOOS have been established, indicating that it serves as an objective tool for assessing knee ligament injuries and knee osteoarthritis within the Indonesian community. KOOS can be used as a measurement of quality of life because it includes measurements of 5 subscales, namely symptoms; rigidity, pain; daily activities; sports and recreation activities and knee-related quality of life. In circumstances one week prior is the period considered when answering the question. Answer options are standard (Likert scale) and each question is scored from 0 to 4. Scores are normalized (a score of 100 indicates no symptoms and 0 indicates extreme symptoms).

Sample size

The following formula estimates the sample size:

$$N = 2\sigma^2 \frac{(Z¿¿1-\alpha/2+Z_{1-\beta})^2}{(\mu 1-\mu 2)^2}¿$$

where *N* is the sample size required in both groups, and *s* is the standard deviation of the primary outcome. This research has a confidence level (1- a) of 95%, so the value obtained is a = 5%. Accordingly, the research hypothesis is unidirectional, so the magnitude of Z1-a = 1.96. The research's power (1-β) was also set at 80%, so the value of β = 20%, then the amount of Z1-β = 0.842. Previous research [18] that analyzed changes in leukocytes in subjects treated with curcuminoid therapy from turmeric extract 30 mg 3 times a day for 14 days, amounting to 30.00 ± 5.10 and meloxicam 1 x 15 mg per day, obtained the mean delta value of leukocytes in the control group was 164.1+50.91 and the treatment group was 174.27+78.93. The total number of respondents required in the 2 groups is 60 people. Considering a dropout rate of 20%, the sample size should be increased to 36 each group.

Ethical Considerations

The ethics research committee has approved the study protocol registered with the Forum for Ethical Review Committees in Asia and the Western Pacific (project number KE-FK-0674-EC-2023). The study was conducted according to Indonesia's 2021 National Health Research and Development Ethical Guidelines and Standards by the Health Research and Development Ethics Committee and the Helsinki Declaration, revised in 2013. Clinical Trials.gov has reviewed this protocol under Registration number: NCT06105840.

Participation of participants in this research was voluntary without any coercion. All participants got information about the research comprehensively especially about the intervention would be given, and the possible benefit and risk. Participants would be allowed to withdraw at any time without penalty.

Participants would be screened and provided a unique ID number to protect their personal information. The unique ID number would be used to differentiate participants in an anonymous manner across measures and follow-up questionnaires. Participants who met the eligibility requirements of the initial screening form would

be prompted to fill out a contact form with their full name and address. Participants would get benefits that are an x-ray examination to know knee joint condition and therapy according to the research provision. Participants would get tools for massage therapy (towel and massage oil) which would be theirs. After research activities had completed, participants in control group would get herbal therapy and acupressure like the treatment group. All information related to identity of research subjects would be kept secret and would be known only by researcher, research staffs, and auditor. Research result would be published without the identity of research subjects.

Adverse events

We conducted an investigation of potential adverse events that could arise with the administration combination of curcuminoid and acupressure therapy, encompassing symptoms such as heightened soreness, pain, numbness, and tingling. All instances of adverse events that pose a threat to life or are associated with a substantial impairment were duly reported to the ethics research committee of the institution. During the research, researcher had provided protection needed if there was something bad happened. The protection given by researcher was the examination by doctor and treatment in hospital.

Data analysis

The baseline characteristics of participants will be assessed using descriptive statistics. The Shapiro-Wilk test will be utilized to determine the normality of the data gathered. Descriptive statistics will be presented using either the mean ± standard deviation or the median (interquartile range), depending on the normality of the data. The Wilcoxon signed-rank test or a Paired T-Test will be employed to do within-group comparisons. In a similar vein, the Mann-Whitney U test or an Independent T-Test will be employed to conduct comparisons between groups. The chosen level of significance for this study will be established at 0.05.

Data management

The collected data will be maintained in a secret manner for the duration of the study and thereafter disposed of after a period of 5 years. The process of collecting initial data will involve the use of printed data-collection forms. These forms will be afterwards organized and transcribed into an electronic format. The electronic data will be saved on a desktop computer that is not connected to the internet, as a precautionary measure to mitigate the risk of illegal access. This stored data will be utilized for further analysis. The individual appointed as the chair of the student project committee at the institute will be responsible for supervising data management.

Results

In June 2023, the capsule formulation was made from turmeric rhizome extract, which had been tested to contain 30 mg of curcuminoids per capsule. The Acupressure technique had also been formulated based on the therapeutic points recorded in the Acupressure Therapy Procedure Module to Improve Comfort in Knee Osteoarthritis which had received copyright from the Ministry of Law and Human Rights of the Republic of Indonesia with ID 000564960. The Sham Acupressure technique had also been determined at points that had the potential to provide benefits relaxing effect on the feet but not at the main point of therapy. Therapeutic procedures and the dosage were checked and approved by all authors.

In September 2023, a total of 84 elderly people who experienced joint pain declared themselves willing to be recruited. Physical examination and radiographs were used to assess participants for Osteoarthritis and there were 72 elderly who met the inclusion criteria. This would allow data analysis to take place in April 2024, and results should be submitted for publication in an international peer-reviewed journal by the end of 2024.

Discussion

The benefits of herbs and acupressure can be helpful to additional options in treating inflammation and pain in patients with osteoarthritis. Curcuminoid is an active compound in turmeric that has natural anti-inflammatory properties. Result of meta-analysis conducted by Kou et all [19] showed that curcuminoid supplementation was effective in reducing clinical symptoms in the treatment of arthritis diseases. The use of curcuminoid supplementation in arthritis patients could reduce the possibility of unpleasant consequence. The result of systematic review showed that acupressure as a single or complementary intervention provides significant benefits in the management of Osteoarthritis. [10]

Several studies showed that curcuminoid supplements may help reduce pain and inflammation in osteoarthritis. Acupressure points can stimulate the release of natural endorphins, which can help reduce pain and increase feelings of relaxation. Acupressure also works to help restore uninterrupted energy flow in the body, which can help reduce inflammation and improve joint function. Therefore, we deliberately choose a RCT design as it is often regarded as the preferred strategy for assessing and comparing the efficacy of therapies.

The strength of this study lies in its ability to prove the efficacy of a combination therapy between curcuminoids and acupressure for osteoarthritis. This is achieved through the use of an RCT design, which has never been proven by other studies before. This study uses RCT because it can

demonstrate the superiority of a new treatment over an existing standard treatment or a placebo. RCT is the gold standard for ascertaining the efficacy and safety of a treatment. After conducting a systematic review [20] , researchers continue research using RCTs in the hope of obtaining empirical evidence with the highest level of evidence with low control of the risk of systematic error (bias). Another advantage of this study is that the respondents used came from identical communities so that they are likely to have homogeneity of demographics and characteristics of respondents needed in RCTs. The limitation of this study is that it does not consider the severity of osteoarthritis or the duration of osteoarthritis.

The main findings of the research expected to achieve biomarker change, which consisted of a decline in inflammatory markers as shown by leukocyte numbers and the neutrophil lymphocyte ratio, a decline in the secretion of the COX-2 enzyme, and an increase in the secretion of endorphin hormones after conducting research interventions for 3 weeks. The secondary outcome was the decline in knee pain, the increase in joint functional ability, activity daily living and quality of life.

Leukocyte count and Neutrophil Lymphocyte Ratio are thought to increase linearly with the severity of Osteoarthritis. The research of Tasoglu et al [21] showed that when the severe Osteoarthritis are high, the blood NLR levels was found to increase as compared to the mild to moderate knee Osteoarthritis group. A blood NLR of ≥2.1 was taken as the cutoff based upon the receiver operating characteristics. In the roc curve analysis, blood NLR≥ 2.1 had 50 % sensitivity and 77 % specificity in predicting severe knee Osteoarthritis. The results of the present study suggested blood NLR as a novel and promising inflammatory marker indicating the severity of knee Osteoarthritis. Blood NLR was a recent indicator of systemic inflammation. A blood NLR≥ 2.1 was an independent risk factor for severe knee Osteoarthritis.

This study sought empirical evidence that COX-2 is expressed in peripheral blood as a result of inflammatory process in osteoarthritis patients. The anti-inflammatory action of curcuminoid-standardised turmeric extract is achieved by inhibiting the activity of cyclooxygenase, lipoxygenase and also by acting as an antioxidant. In vitro curcuminoid can inhibit the activity of phospholipase, lipoxygenase, cyclooxygenase-2, leukotriene, prostaglandin, thromboxane, NO, collagenase, elastase, hyaluronidase, interferon, tumor necrosis factor alpha and interleukin-12. [22]

In addition to COX-2 and NLR, the endorphin hormone was measured as a biomarker in this study. Pain changes experienced by sufferers of genu osteoarthritis can be secreted into the blood. The more

endorphin enzymes secreted by monocytes into the blood, the less pain will occur and the more comfort.

Knee pain is an unpleasant sensory and emotional experience due to potential or actual tissue damage in osteoarthritis. Pain is caused by the stimulation of chemical mediators such as histamine, bradykinin, acetylcholine, and prostaglandins substance. In addition to substances that can stimulate pain sensitivity, the body also has substances that can be inhibit pain. Endorphins and encephalin can relieve the pain. Osteoarthritis pain is associated with severe inflammation and joint disfigurement. The more severe the inflammation and the joint changes, the more painful of joint becomes.

Joint stiffness and joint functional ability are related to pain and inflammation in osteoarthritis patients. The more severe the inflammation and pain, the more joint stiffness increases and joint functional ability declines. Pain is a significant factor in determining an individual's perceived breakpoint, which in turn affects other aspects of life. The most prevalent symptom combinations are joint locking, knee swelling and stiffness. Mobility limitation and the need for assistance increase as a result of pain and limited mobility. Another functional activity affected by limited functional mobility is the ability to perform self-care. [23]

Quality of life is related to pain and activity ability. The more severe the pain and the inability to do activities, the lower the quality of life. The prolonged experience of pain in patients with osteoarthritis represents a "breakpoint," a pivotal point in the experience of living with unrelenting pain, mobility limitations, and the subsequent consequences for physical and psychological well-being. These breakpoints experienced by Osteoarthritis patients are turning points for changes in quality of life in Osteoarthritis. This turning point is precipitated by an increase in pain; the emergence of a combination of other symptoms; an increased limitation or loss of mobility; and changes in other functional activities. [10]

Conclusions

This document outlines a randomized clinical experiment that aims to examine and compare the impacts of curcuminoid and acupressure interventions on the enhancement of inflammation, pain, and quality of life among elderly diagnosed with osteoarthritis.

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Data Availability

The data sets generated during this study were available from the corresponding author on reasonable request

Conflicts of Interest

None declared.

Author Contributions

SM contributed to data curation, formal analysis, investigation, writing the original draft, review, and editing. NK contributed to conceptualization, project administration, resources, supervision, methodology, review, and editing. EM contributed to conceptualization, data curation, formal analysis, investigation, review, and editing

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Abbreviations

CAM : Complementary Alternative Medicine

COX-2 : Cyclooxygenase-2

ELISA : Enzyme Linked Immunosorbent Assay

KOOS : Knee injury and Osteoarthritis Outcome Score

NLR : Neutrophil Lymphocyte Ratio

RCT : Randomized Controlled Trial

WOMAC : The Western Ontario and McMaster Universities Osteoarthritis Index

Supplementary Files

Figures

Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

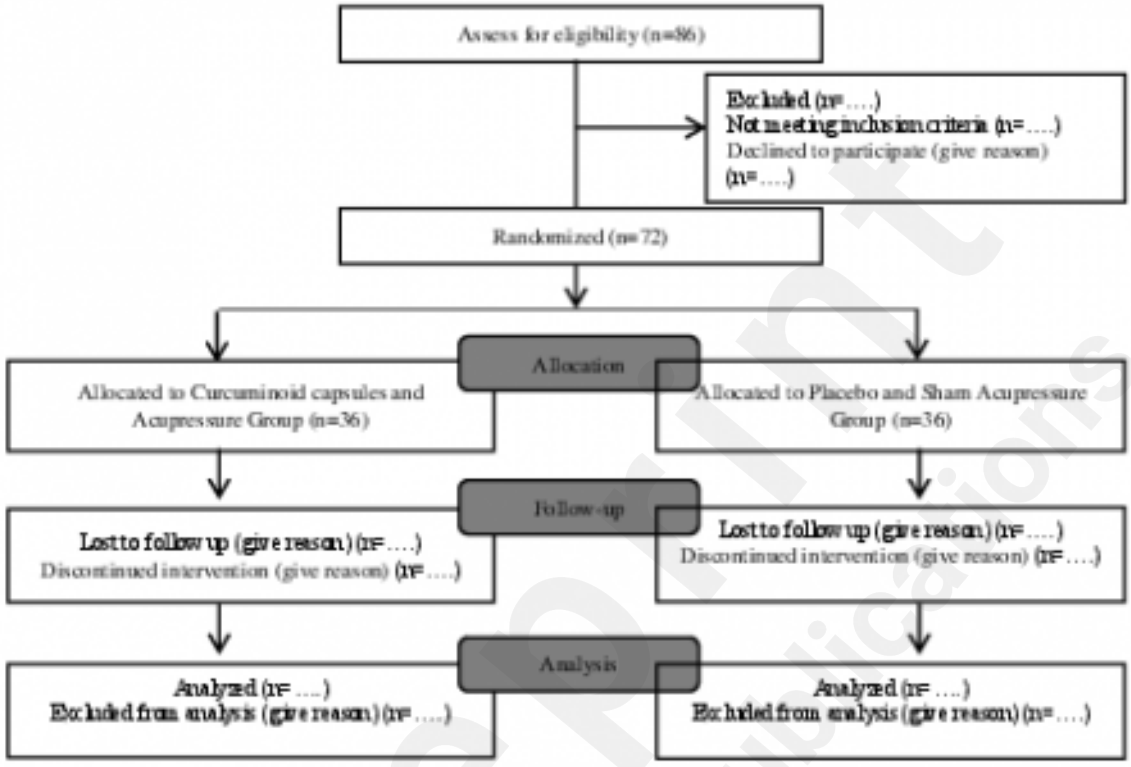

Figure 1. Schematic CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommended schedule for participation.

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation			Close-out			
TIMEPOINT**		0	1st week	2nd week	3rd week	1st day	1st week	2nd week	Post 3rd week
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
[Radiography and MMSE Test]	X								
Allocation		X							
INTERVENTIONS:									
[C+A Therapy]			X	X	X				
[P+S Therapy]			X	X	X				
ASSESSMENTS:									
[Demographic Details]	X								
[Inflammatory Marker]						X			X
[Endorphin]						X			X
[Quality of Life]						X	X	X	X

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommended schedule for participation.

Related publication(s) - for reviewers eyes onlies

Ethical Approval from Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) (project number KE-FK-0674-EC-2023).
URL: http://asset.jmir.pub/assets/67d0fe712254f9f5ffdbee14761f7710.pdf

Registration number from Clinical Trials.gov : NCT06105840.
URL: http://asset.jmir.pub/assets/7d4b5d7ce8815fa2d27e28db9a6d139f.pdf